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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Customer No.	23643
Group:	1617
Confirmation No.:	7025
Application No.:	10/050,289
Invention:	METHOD OF TREATMENT OF DOPAMINE-RELATED DYSFUNCTION
Inventor:	David E. Nichols et al.
Filed:	January 16, 2002
Attorney Docket:	3220-69768
Examiner:	KIM. JENNIFER M.

Certificate Under 37 CFR 1.8(a)

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

on January 15, 2004

(Signature)

Joyce Hamilton

(Printed Name)

DECLARATION UNDER 37 C.F.R. § 1.132 OF DR. RICHARD B. MAILMAN

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I declare as follows:

1. I am currently the Director of the Division of Basic Psychobiology, Chief of the Molecular Pharmacology Section, and a Professor of Psychiatry, Pharmacology, and Medicinal Chemistry, in the Department of Psychiatry at the University of North Carolina School of Medicine, Chapel Hill, North Carolina. I received a Doctorate of Physiology degree (Ph.D.) from the North Carolina State University, Department of Physiology, in 1974. My research interests have included molecular and cellular neuropharmacology and neurotoxicology. I have authored or co-authored more than 150 peer-reviewed journal articles, more than 50 book

chapters, and two books in the areas of my research interest. A copy of my curriculum vitae is attached as Exhibit A.

2. I have read and understand the specification of the captioned application, the claims as they have been amended, and the Office Action dated July 15, 2003. I understand that in the office action dated July 15, 2003, in the captioned patent application, the Examiner rejected claims 1-12 as being unpatentable because, according to the Examiner, the application does not enable the use of any full D_1 agonist except dinapsoline, administered using the intermittent dosing protocol described and claimed in the captioned patent application, to treat a patient with Parkinson's disease resulting from a dopamine-related dysfunction.

3. I respectfully disagree with the Examiner. The captioned application describes a dosing protocol that is applicable to a wide variety of full D_1 agonists, regardless of chemical class, providing that those agonists have a half-life of less than 6 hours. Furthermore, dinapsoline is representative of those compounds falling within the scope of full D_1 agonists having half-lives of less than 6 hours and which are effective to treat a patient with Parkinson's disease resulting from a dopamine-related dysfunction using the claimed intermittent dosing protocol.

4. Claims 1-12 of the captioned patent application are directed to a method for treating a dopamine-related disorder using an intermittent dosing protocol, wherein at least once every 24 hours, the dose of the agonist is reduced to obtain a plasma concentration that results in suboptimal activation of D_1 dopamine receptors for a period of time sufficient to prevent the induction of tolerance.

5. The specification of the captioned application describes how to carry out the claimed intermittent dosing protocol using dinapsoline to treat a patient with Parkinson's disease resulting from a dopamine-related dysfunction.

6. For example, the specification of the captioned application contains Examples (*see, e.g.*, Figure 4 and Example 7) showing that when dinapsoline is administered according to the claimed method, tolerance is not observed, and when dinapsoline is not administered

according to the claimed method, e.g. via a minipump over 24 hours (*see* Figure 6), tolerance is observed.

7. D_1 agonists from many chemical classes can induce tolerance if not administered according to the claimed intermittent dosing protocol, as illustrated in Figure A below. In Figure A, dinapsoline (DNS) is an isoquinoline, A77636 is an isochroman, and dihydrexidine (DHX) is a benzophenanthridine. These three D_1 agonists are from different chemical classes, and each induced tolerance when not administered according to the claimed method. The tolerance observed in Figure A was evaluated by comparing the response to the challenge dose in the minipump-treated animals with the response to the challenge dose in naïve animals ($p<0.01$ when comparing solid to hatched bars).

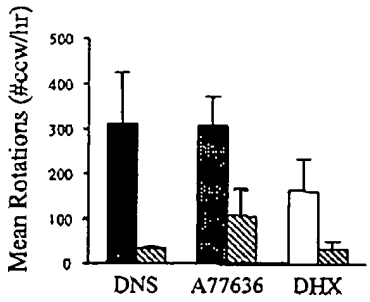

Figure A. Solid bars represent the response to a challenge dose in naïve animals; hatched bars indicate the response to a challenge dose in animals treated with the same D_1 agonist for 24 h via a minipump.

8. Dihydrexidine is a full D_1 agonist having a half-life of less than 6 hours. When dihydrexidine was dosed via a minipump for 24 hours (24 mg/kg/day), tolerance was induced to a challenge dose of dihydrexidine (1 mg/kg) given ca. 2.5 hours later, as illustrated in Figure B (top panel). The tolerance observed in Figure B (top panel) was evaluated by comparing the response to the challenge dose of dihydrexidine in the minipump-treated animals with the response observed during minipump treatment of those animals ($p>0.05$ when comparing challenge response to baseline).

9. When dihydrexidine was dosed via a minipump for 20 hours (24 mg/kg/day), tolerance was not induced to a challenge dose of dihydrexidine (1 mg/kg) given ca. 2.5 hours

later, as illustrated in Figure B (bottom panel). The tolerance observed in Figure 2 (bottom panel) was evaluated by comparing the response to the challenge dose of dihydrexidine in the minipump-treated animals with the response observed during minipump treatment of those animals ($p<0.001$ when comparing challenge response to baseline).

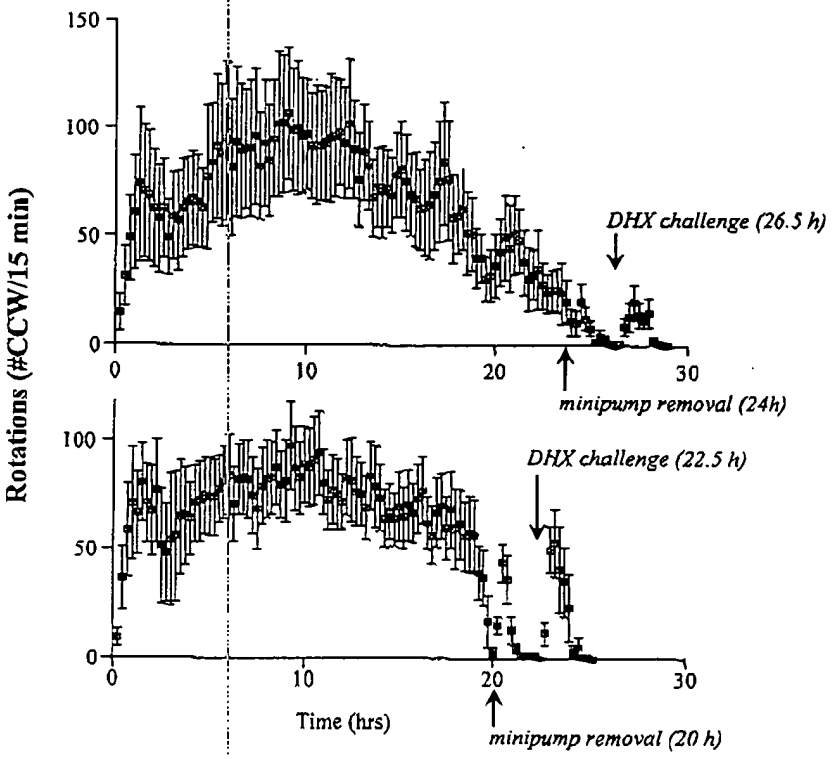

Figure B.

10. Dihydrexidine was evaluated according to the experimental design described in the specification of the captioned application. Accordingly, the data in Figures A and B do not support the Examiner's contention that the captioned application does not enable the use of any full D_1 agonist except dinapsoline administered using the intermittent dosing protocol described in the captioned patent application to treat a patient with Parkinson's disease resulting from a dopamine-related dysfunction. The data in Figures A and B demonstrate that the captioned application does enable the use of full D_1 agonists, even those from different chemical classes, administered using the claimed method, to treat a patient with Parkinson's disease resulting from a dopamine-related dysfunction. Furthermore, only routine experimentation was required to determine the reduced dose of dihydrexidine required to obtain a second lower tissue

concentration of agonist, upon minipump removal, that resulted in suboptimal activation of D_1 dopamine receptors for a period of time sufficient to prevent induction of tolerance. Similarly, when dinapsoline was administered continuously via a minipump (6 mg/kg/day), tolerance was induced in treated animals within 24 hours, as illustrated in Figure C (top panel).

11. When dinapsoline was administered thrice daily via subcutaneous injections (2 mg/kg) tolerance was induced in treated animals within 24 hours, as illustrated in Figure C (middle panel).

12. When dinapsoline was administered twice daily via subcutaneous injections (2 mg/kg) tolerance was not induced in treated animals within 24 hours, as illustrated in Figure C (bottom panel).

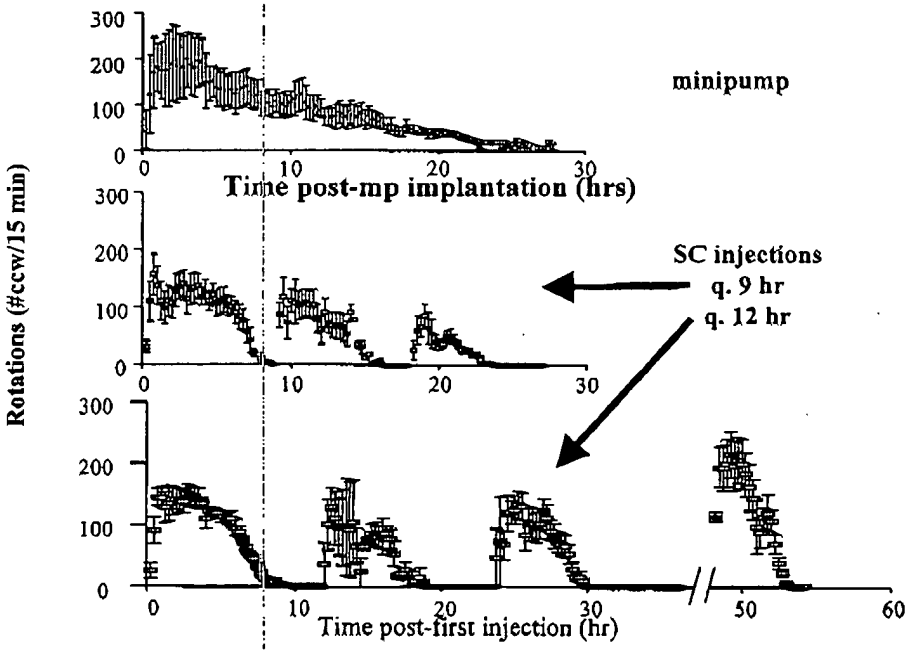

Figure C.

13. When dinapsoline was administered once daily via a subcutaneous injection (2 mg/kg) tolerance was not induced in treated animals (*see* Figure 4 and Example 7 in the captioned application).

14. The required reduced dose of the D_1 agonist, the suboptimal activation of D_1 dopamine receptors, and the period of time sufficient to prevent induction of tolerance were

obtained by dosing the animals (6-OHDA-lesioned rats), as described in the specification of the captioned application, one or more times per day until tolerance was observed. In the case of dinapsoline, only three experiments were required to determine those doses (i.e. resulting from a dosing protocol) that were required to prevent the induction of tolerance.

15. The data in Figure C above and in Figure 4 of the specification do not support the Examiner's contention that undue experimentation is required to determine the reduced dose of the D_1 agonist required at least once every 24 hours that results in suboptimal activation of D_1 dopamine receptors for a period of time sufficient to prevent induction of tolerance.

16. The data presented in this declaration demonstrate that the specification of the captioned patent application enables the use of full D1 agonists, even from different chemical classes, administered using the claimed method to treat a patient with Parkinson's disease resulting from a dopamine-related dysfunction. The data also demonstrates that only routine experimentation is required to determine the reduced dose of a D_1 agonist that results in the suboptimal activation of dopamine receptors, and to prevent the induction of tolerance.

All statements herein made of my own knowledge are true, and all statements herein made on information and belief are believed to be true; these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code; and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

Dated: January 15, 2004

15 January 2004

By:

Richard B. Mailman, Ph. D.